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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/434,708	11/05/1999	HAMID BAND	B0801/7159(E	4277

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EXAMINER
EWOLDT, GERALD R

ART UNIT	PAPER NUMBER
1644	18

DATE MAILED: 04/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/434,708	Band et al.
Examiner	**Art Unit**
G.R. Ewoldt	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 22, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7, 9, 11, and 50* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-7, 9, 11, and 50* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/22/02 has been entered.

2. Claims 1-7, 9, 11, and 50 are pending and being acted upon.

3. New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections. Applicant is required to submit acceptable corrected drawings <u>within the time period set in the Office action</u>. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

4. In view of Applicant's amendment, filed 1/22/02, the previous rejections under 35 U.S.C. 112, first paragraph (new matter) and 35 U.S.C. 112, second paragraph, have been withdrawn.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7, 9, 11, and 50 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

an isolated nucleic acid molecule consisting of SEQ ID NO:1 or SEQ ID NO:3, or a nucleic acid molecule that differs from said nucleic acid molecules due to the degeneracy of the genetic code, or complements of said nucleic acid molecules, does not reasonably provide enablement for:

A) an isolated nucleic acid molecule which hybridizes to SEQ ID NO:1 under stringent conditions and which codes for a polypeptide that binds a tyrosine kinase and downregulates its expression, or

B) an isolated nucleic acid molecule consisting of a unique fragment of SEQ ID NO:1 or a fragment of SEQ ID NO:3, or

C) an isolated nucleic acid molecule consisting of 2-200 contiguous nucleotides of SEQ ID NO:1, or

D) an isolated nucleic acid molecule which is a fragment of SEQ ID NO:1 which encodes a polypeptide which is immunogenic, or

E) a pharmaceutical composition comprising an isolated nucleic acid molecule consisting of SEQ ID NO:1 or an expression product thereof.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Applicant asserts the nucleic acids of SEQ ID NOS:1 and 3 "make it possible for the artisan to diagnose a disorder characterized by an aberrant [including mutant] expression of cbl-SL," and further asserts the nucleic acids of the instant claims can be used in a "method for treating subjects expressing a mutant cbl-SL," presumably through an association of cbl-SL with tyrosine kinases. Applicant further asserts that aberrant cbl-SL expression is associated with essentially every known cancer (see page 28, lines 11-24). However, the specification discloses insufficient evidence (i.e., working examples) of *any* association between aberrant expression of cbl-SL and *any* cancer. Thus, in view of the factors cited above, given the nature of the invention (a product for the treatment and diagnosis of cancer which must be considered highly unpredictable given the unpredictable nature of cancer), the state of the prior art (it is acknowledged in the specification that "little is known" about the regulation of cellular tyrosine kinases), and the amount of direction provided by the inventor (essentially none for the intended use), said diagnosis or treatment would be highly unpredictable and require undue experimentation. While the nucleic acids of the instant claims appear to encode a polypeptide which associates with the EGF receptor and appears to be capable of downregulating phosphorylation of said receptor, the single *in vitro* example demonstrating said association (Example 6) is insufficient to enable the invention of the instant claims in their entire breadth.

The instant claims encompass variants (nucleic acids which hybridize under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1) and fragments of the nucleic acids of SEQ ID NOS:1 and 3 which encode polypeptides comprising variants and fragments of SEQ ID NO:2. The claims as recited encompass nucleic acid molecules that encode a virtually unlimited number of polypeptides. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (of record) teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. teaches further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (see Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (of record), teaches that a single Glu

to Val substitution in the subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (see pages 126-128, section 6-3A and page 230, paragraph bridging columns in particular). Further, the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, of record). Thus, the combined references serve to demonstrate that predicting the function of polypeptides comprising "deletions, additions, and substitutions", as well as polypeptides encoded by nucleic acids "which hybridize under stringent conditions" is highly uncertain and would require undue experimentation. Additionally, the claims recite fragments as small as 2 nucleotides long, said fragments would be too small to even encode a polypeptide and thus, could not be enabled for any use.

Note that a sequence which hybridizes to SEQ ID NO:1 would be its complementary DNA sequence. A polypeptide encoded by said complementary DNA sequence would not encode a polypeptide that binds a tyrosine kinase, but rather a random collection of amino acids. Said random collection of amino acids would be unlikely to function as claimed and would thus be considered highly unpredictable. Said unpredictability would necessitate undue experimentation as there would be no particular expectation of success. Also note that a nucleic acid which actually encodes a polypeptide that binds a tyrosine kinase and downregulates its expression must be considered highly unpredictable. While the specification discloses that the polypeptide encoded by SEQ ID NO:2 associate with the EGF receptor in an unknown fashion, there is no demonstration or evidence to indicate that the polypeptide encoded by SEQ ID NO:2 binds any tyrosine kinase. Further, as "expression" of a protein is defined as transcription and translation of said protein, it is unclear how the binding of an existing protein would affect its already-occurred transcription and translation.

Regarding claims drawn to immunogenic fragments or pharmaceutical compositions, *in vivo* enablement is required for an intended *in vivo* use. Pharmaceutical uses include the *in vivo* diagnosis, prevention, treatment, or cure of a disease or

condition. As noted above, the specification discloses no *in vivo* demonstrations of the claimed invention being used for the treatment or diagnosis of cancer. Note that the single disclosed species of an immunogenic fragment (SEQ ID NO:10) is insufficient to enable a claim to all possible immunogenic fragments including fragments encompassed by the claim that would be too small to actually be immunogenic. As no working examples demonstrating enablement for any *in vivo* uses of the claimed invention are disclosed, the instant invention must be considered highly unpredictable and requiring of undue experimentation to practice as claimed.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 1/22/02, have been fully considered but have not been found persuasive. Applicant argues that "Applicants provided [said] references to show how important the regulation of tyrosine kinase expression is in the field of cancer. Applicants teach cbl-SL nucleic acids and polypeptides, and that cbl-SL polypeptides bind and downregulate tyrosine kinases. Applicants provide sufficient guidance to one of ordinary skill in the art on how to make and regarding how to make and use the cbl-SL polypeptides encoded by the claimed nucleic acids of the present invention." It is the Examiner's position that while the regulation of tyrosine kinases may be important in the field of cancer, Applicant's demonstration that a single polypeptide encoded by a single nucleic acid of the instant claims "associates" with a single growth receptor is insufficient support for all the nucleic acids encompassed by the instant claims.

Applicant argues that *in vivo* data is not required and the single *in vitro* example is sufficient to enable the claimed invention. It is the Examiner's position that the single *in vitro* example is insufficient to enable the breadth of the claimed invention for the reasons of record, as set forth in Paper Nos. 12 and 14, mailed 1/02/01 and 6/01/01 respectively, and the reasons set forth above.

7. Claims 1-7, 9, 11, and 50 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that Applicant was in possession of any cbl-SL nucleic acid fragments, unique fragments or compliments thereof; or cbl-SL nucleic acid molecules consisting of sequences of 2-7, 8, 10, 12, 14, 16, 18, 2,0, 22, 24, 26, 28, 30, 50, 75, 100, or 200 contiguous nucleotides of fragments, unique fragments or compliments of the nucleic acids of SEQ ID NOS:1 or 3, other than SEQ ID NOS:1 or 3. Neither is there sufficient written description to show that Applicant was in possession of a nucleic acid encoding polypeptides consisting of immunogenic fragments of SEQ ID NO:1, other than a nucleic acid encoding the peptide of SEQ ID NO:10. The instant claims encompass a virtually unlimited number of nucleic acids while the specification discloses just 2. Note that the specification discloses no nucleic acids comprising the functional language of Claim 1, i.e. a nucleic acid which encodes a polypeptide that binds a tyrosine kinase and downregulates its expression for reasons set forth in paragraph 6 above. One of skill in the art would therefore conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

Applicant has not addressed the rejection separately. See Examiner's response in paragraph 6 above.

8. No claim is allowed.

9. SEQ ID NOS:1 and 3 appear to be free of the prior art.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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Technology Center 1600
April 4, 2002